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# **Effectiveness of a multifaceted intervention on potentially inappropriate prescribing in older patients in primary care: a cluster randomised controlled trial (the OPTI-SCRIPT study)**

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## **Abstract**

**Purpose:** Potentially inappropriate prescribing (PIP) is common in older people and can result in increased morbidity, adverse drug events and hospitalisations. This study tested the effectiveness of a multifaceted intervention in reducing PIP in primary care.

**Methods:** A cluster randomised controlled trial (RCT) was conducted with 21 GP practices and 196 patients with PIP. Intervention participants received a complex multi-faceted intervention incorporating academic detailing, medicines review with web-based pharmaceutical treatment algorithms that provide recommended alternative treatment options, and tailored patient information leaflets. Control practices delivered usual care and received simple, patient-level PIP feedback. Primary outcomes were the proportion of patients with PIP and the mean number of potentially inappropriate prescriptions. Intention-to-treat analysis using random effects regression was used.

**Results** All practices and 190 patients were followed. Upon intervention completion, patients in the intervention group had significantly lower odds of having PIP than patients in the control group (adjusted odds ratio (OR) 0.32, 95% confidence interval (CI) 0.15 to 0.70,  $P=0.02$ ). The mean number of PIP drugs in intervention was 0.70, compared to 1.18 in control ( $P=0.02$ ). The intervention group was almost a third less likely than control to have PIP drugs at intervention completion, but this was not significant (incidence rate ratio 0.71, 95% CI 0.50 to 1.02,  $P=0.49$ ). The intervention was effective in reducing proton pump inhibitor prescribing (adjusted OR 0.30, 95% CI 0.14 to 0.68,  $P=0.04$ ).

**Conclusions** The OPTI-SCRIPT intervention incorporating academic detailing with a pharmacist and medicines' review with web-based pharmaceutical treatment algorithms,

was effective in reducing PIP, particularly in modifying prescribing of proton pump inhibitors, the most commonly occurring PIP nationally.

**Trial Registration:** Current controlled trials ISRCTN41694007

**Key words:** randomised controlled trial, potentially inappropriate prescribing, primary health care

**Abbreviations:** A&E (accident and emergency); ADEs (adverse drug events); BMQ (Beliefs about Medicine Questionnaire); CDSS (computerised decision support systems); CI (confidence interval); CME (continuing medical education); GP (general practitioner); HRB (Health Research Board); HRQOL (health related quality of life); ICC (intraclass correlation coefficient); ICGP (Irish College of General Practitioners); IRR (incidence rate ratio); NSAID (Nonsteroidal anti-inflammatory drug); OR (odds ratio); PCRS (Primary Care Reimbursement Services); PIP (potentially inappropriate prescribing); QUB (Queen's University Belfast; RCSI (Royal College of Surgeons in Ireland); RCT (randomised controlled trial); Rx-PAD (Prescription Peer Academic Detailing); TCA (Tricyclic Anti-depressant); WBQ-12 (Well-being Questionnaire)

## INTRODUCTION

Older people tend to have multimorbidity with consequent polypharmacy, making prescribing in this population challenging, with the potential for adverse outcomes including drug-drug interactions and adverse drug events (ADEs).<sup>1,2</sup> Potentially inappropriate prescribing (PIP) describes a number of suboptimal prescribing practices particularly the use of medicines that introduce a greater risk of ADEs where a safer, as effective alternative is available to treat the same condition.<sup>3,4</sup> PIP in older people is common across healthcare settings and can result in increased morbidity, ADEs and hospitalisations.<sup>2,5,6</sup> In Ireland, 36% of those aged  $\geq 70$  years received at least one potentially inappropriate prescription in 2007, with an associated expenditure of over €45 million.<sup>7</sup> PIP in community-dwelling older Irish people is associated with increased ADEs, accident and emergency (A&E) visits, and poorer health related quality of life (HRQOL).<sup>8</sup>

Interventions targeting PIP represent an important public health measure, particularly in primary care where the majority of prescribing takes place. There is no one interventional strategy that has proved to be most effective.<sup>9</sup> A number of commentators have argued that a multifaceted intervention, which combines a number of techniques within a single intervention,<sup>10</sup> may be more likely to improve prescribing than any one single intervention.<sup>11,12</sup> To date, a limited number of multifaceted interventions have been evaluated in primary care to decrease PIP.<sup>13,14</sup>

The purpose of the OPTI-SCRIPT study (OPTImizing PreSCRIBing for Older People in Primary Care, a clusTer randomised controlled trial) was to investigate the effectiveness of a multifaceted intervention in reducing PIP in older people in Irish primary care.

## **METHODS**

A cluster randomised controlled trial (RCT) was conducted in Irish primary care to alter general practitioner (GP) PIP-related prescribing following the CONSORT guidelines.<sup>15</sup> The study protocol and intervention development have been detailed previously.<sup>16,17</sup> The Research Ethics Committee of the Irish College of General Practitioners (ICGP) approved the study.

### **Recruitment and randomisation**

GP practices from the Health Research Board (HRB) Centre for Primary Care Research network were invited to participate by email with a follow-up phone call. Practices were eligible if they had at least 80 patients aged  $\geq 70$  years and were based in greater Dublin. Consenting practices were instructed to randomly select 50 patients aged  $\geq 70$  years with capacity to provide informed consent. Prescriptions of these patients were assigned a study ID and sent to the research team where the research pharmacist determined if they had PIP (Appendix 1).<sup>16</sup> Eligible patients were sent study information packs by the GP practice and those wishing to participate returned signed consent forms to the research team.

Baseline data were collected prior to allocation. Practices were allocated to intervention and control by an independent researcher using minimisation (Minimpy<sup>18</sup>), an allocation method commonly used in cluster RCTs to ensure balanced allocation of important cluster level attributes such as practice size when cluster numbers are small. It was not possible to blind patients or GPs to allocations, however, the outcome assessor was blinded.

### **Intervention and control groups**

The multifaceted intervention involved academic detailing with a pharmacist on how to conduct GP-led medicines review with participating patients; medicines reviews were supported by web-based pharmaceutical treatment algorithms for GPs providing evidence-based alternative treatment options to PIP drugs; and tailored patient information leaflets, (Table 1 and Appendix 2) <sup>16</sup> The intervention was delivered from October 2012 to

September 2013. Control practices delivered usual care and received one-off simple patient-level PIP feedback (Table 1).

## **Outcomes**

Outcome data were collected upon intervention completion (i.e. point at which all reviews were completed in a practice) at approximately 4-6 months following baseline data collection.

### *Primary outcomes*

Two primary outcomes were used, firstly, the proportion of patients with PIP drugs (a composite measure, i.e. any number of PIP drugs as included in the study to address multiple PIP in individual patients). Secondly, the mean number of PIP drugs per group was investigated. PIP was determined for intervention and control groups from a review of prescriptions by a research pharmacist (Appendix 1).

### *Secondary outcomes*

Secondary outcomes included individual measures of the composite measure, i.e. drug-specific outcomes, including the absolute number of PIP drugs per group of the top five reported nationally:<sup>7</sup> proton pump inhibitor at full therapeutic dosage for >8 weeks, long-term (>3 months) use of non-steroidal anti-inflammatories (NSAIDs), long-term (>1 month) use of long-acting benzodiazepines, therapeutic duplication and tricyclic antidepressants (TCAs) with an opiate or calcium channel blocker. Patient-reported outcomes included the Patients' Beliefs about Medicines Questionnaire (BMQ),<sup>19</sup> and the Well-being Questionnaire (WBQ-12)<sup>20</sup> collected via self completed questionnaires.

## **Sample size calculation**

A sample of at least 22 practices and 220 patients was required, incorporating the effects of cluster randomisation and a 10% loss to follow-up. The calculation was based on both



primary outcomes. The calculation for the proportion of participants with PIP was based on demonstrating a clinically relevant 10% absolute reduction (from 100% to 90%) in the proportion of PIP, with 80% power and a statistical significance of 5% (1-sided), between randomised groups. For the mean, the calculation was based on demonstrating a 30% relative reduction in the mean number of potentially inappropriate prescriptions in the intervention group compared to the control group (equivalent to a mean reduction of 1.02 inappropriate prescriptions), with 80% power and a statistical significance of 5% (2-sided).<sup>17</sup>

## **Analysis**

Data analysis was by intention to treat.

### *Primary outcomes*

Separate approaches were used to analyse the two primary outcomes. The proportion of patients with PIP is presented and was analysed using a random effects logistic regression with the individual as the unit of analysis and the practice included as the random effect, to control for the effects of clustering. Baseline covariates (age, gender, baseline number of PIP drugs, baseline number of repeat medications) and minimisation factors (number of GPs, practice location) were included in the model.

The mean number of PIP drugs was calculated per group, as specified in the study protocol, and a mean difference calculated using a cluster level t-test.<sup>17</sup> However, preliminary analyses indicated that the data were skewed. The median number of PIP drugs was additionally investigated and skewness was addressed using a random effects Poisson regression, presenting incidence rate ratios (IRRs). Again, the individual was the unit of analysis and the practice was included as the random effect, and baseline covariates and minimisation factors were included. The Bonferroni correction was used to adjust for multiple comparisons.

### *Secondary outcomes*

Random effects logistic regressions were used to test the differences in drug-specific secondary outcomes between intervention and control and random effects multiple regressions were conducted for the patient-reported outcomes.

### **National contemporaneous comparison group**

The control group may have changed their prescribing behaviour due to the reactive effects of being studied (Hawthorne effect) and receiving simple feedback.<sup>21,22,23</sup> In anticipation of this, anonymised data from the Primary Care Reimbursement Service (PCRS) pharmacy claims database of dispensed medications (national prescribing database of GP and pharmacy claims)<sup>24</sup> were analysed, acting as a national contemporaneous comparison group. National PCRS prescribing data for those aged  $\geq 70$  years from September 2012 to August 2013, were analysed and the following data retrieved:

1. Number of people with PIP
2. Number of people with no PIP
3. Decreases in the number of PIP drugs
4. PIP that remained the same.

PIP was assessed using 28 criteria included in this study,<sup>16</sup> (six of the PIP criteria could not be applied as the PCRS data lacked the detailed information needed).

From these figures, crude odds ratios (ORs) were calculated, comparing the OPTI-SCRIPT intervention and control groups to the national PCRS comparator.

## RESULTS

Figure 1 displays the flow of participants through the RCT. In total 21 GP practices and 196 patients were recruited. All GP practices and 190 (97%) patients were followed up on intervention completion. Practices and patients were similar at baseline but the control group were situated in more socioeconomically deprived areas (Table 2). Proton pump inhibitors at maximum therapeutic dosage > 8 weeks was the most frequently occurring PIP in both groups (Table 3).

### Primary outcomes

Upon intervention completion, the proportion of patients with PIP drugs was 0.52 in intervention compared to 0.77 in control. Participants in the intervention group had significantly lower odds of having PIP than those in the control group (adjusted OR 0.32, 95% confidence interval (CI) 0.15 to 0.70,  $P=0.02$ ) (Table 4).

The mean number of PIP drugs in the intervention group was 0.70, compared to 1.18 in the control group ( $P=0.02$ ). The median was 1 in both intervention and control.

Investigating the number of PIP drugs per person using Poisson regression, patients in the intervention group were estimated to have 29% less PIP drugs than patients in the control group, but this was not significant at the 5% level (IRR 0.71, 95% CI 0.50 to 1.02,  $P=0.49$ ) (Table 4).

### Secondary outcomes

#### *Drug specific outcomes*

At intervention completion, participants in the intervention group had significantly lower odds of having a potentially inappropriate proton pump inhibitor compared to those in the control group (adjusted OR 0.30, 95% CI 0.14 to 0.68,  $P=0.04$ ). No statistically significant differences were found for other drug-specific outcomes (Table 5). In the intervention group, 50% of potentially inappropriate proton pump inhibitors were amended by dose

reduction to maintenance level, 20% were stopped completely, 11% were switched to an alternative (e.g. H<sub>2</sub> antagonist) and 20% were unaltered.

#### *Patient reported outcomes*

For the patient reported outcomes of well-being and beliefs about medication, no statistically significant differences were found after completion of the intervention (Table 5).

#### **National contemporaneous comparison group**

Participants in the OPTI-SCRIPT intervention group had lower odds of having PIP compared to those in the national comparator group (crude OR 0.4, 95% CI 0.3 to 0.6) and were more likely to have a decrease in the number of PIP drugs, than the national comparator group (crude OR 2.5, 95% CI 1.8 to 4.0) (Table 6).

## DISCUSSION

The OPTI-SCRIPT intervention was effective in reducing PIP. However, this effect was mediated principally through reducing prescriptions of proton pump inhibitors at maximal dose, the most commonly encountered study PIP.

Previous studies aimed at reducing PIP have been focused in hospital and nursing home settings.<sup>25-27</sup> A limited number of RCTs to reduce PIP specifically in primary care have been conducted. Of those interventions that have been evaluated, single interventions such as computerised decision support systems (CDSSs), educational interventions and multidisciplinary teams have produced inconsistent effects.<sup>2,28,29</sup> Multifaceted interventions may be more likely to improve prescribing than single interventions.<sup>11,12</sup>

Our results are consistent with two separate RCTs published since the start of the OPTI-SCRIPT study in finding a multifaceted intervention to be effective.<sup>13,14</sup> Rognstad et al. found peer academic detailing, delivered at continuing medical education (CME) meetings, with mailed prescriber feedback, produced a 10% (95% CI 5.9 to 15.0) reduction in PIP in the Rx-PAD study.<sup>14,30</sup> Bregnhøj et al. found interactive educational meetings and feedback resulted in a 5-point (95% CI -7.3 to -2.6) improvement in the medication appropriateness index (MAI) score.<sup>13</sup> Differences in effect sizes reported between these studies and the OPTI-SCRIPT findings may arise from a number of factors including differences in the criteria used to assess PIP, the duration of follow-up and the included patients.

An important difference may also be the intensity of the intervention. OPTI-SCRIPT was more intensive, delivering academic detailing face-to-face, rather than a group setting. During the medication reviews, GPs were provided directly with patient-specific lists of PIP drugs and advice on medication changes via the web-based pharmaceutical treatment algorithms, feasibly, having a larger effect size as it encouraged an immediate action to be taken rather than providing educational support or information.

Changes in prescribing of particular drugs can be responsible for the overall effectiveness of interventions.<sup>31</sup> The OPTI-SCRIPT intervention primarily impacted on proton pump inhibitors

prescribing which was highly prevalent at baseline (60%). No impact on therapeutic duplication or benzodiazepine use was found. This is likely due to the small numbers of patients exposed to these PIP drugs. However, this may also reflect the different challenges of modifying medicines as opposed to altering dosage regimes, particularly with benzodiazepines, whose tolerance levels result in interventions to improve prescribing having varying success.<sup>32</sup> There is a concern that discontinuation of benzodiazepines in this population may produce more harm than benefit and patients may be reluctant to discontinue.<sup>33,34</sup> OPTI-SCRIPT GPs, may have been more comfortable altering proton pump inhibitors than benzodiazepines. Based on the low number of benzodiazepines in this study, we cannot be certain that the OPTI-SCRIPT intervention would be effective in reducing prescribing of these medications.

The OPTI-SCRIPT intervention was not found to impact on patients' sense of well-being and beliefs about medicine. The sample size may have been too small and the follow-up period too short to detect a difference in patient reported outcomes, a common criticism of prescribing interventions.<sup>28</sup> It is possible that beliefs about medicines may have been more likely to change than patients' well-being given the short follow-up period, however, evidence indicates that beliefs about medicines remain stable over time, irrespective of changes in health status.<sup>35</sup> Overall, these results suggest that modifications in proton pump inhibitors dosage do not appear to affect patient's sense of well-being or concerns.

### **Strengths and limitations**

Strengths of this study include a rigorous design of a clinically relevant intervention,<sup>16</sup> high retention rates (primarily due to the nature of the outcome data and the short follow-up period), completeness of the prescription data and being conducted in a primary care setting using existing resources. Selection bias was minimised by collecting baseline data prior to minimisation, which was carried out by an independent third party. Owing to the nature of the intervention, it was not possible to blind patients or GPs to allocations, however, the outcome assessor was blinded to allocation,

The intervention was effective at decreasing the most prevalent PIP (proton pump inhibitors) in this study. The more frequent an outcome is, the greater the potential the OR will over or under estimate the relative risk (RR). Using methods proposed by Zhang et al<sup>36</sup>, we explored this and found little difference between the OR (0.32) and the RR (0.38), increasing confidence in the study findings.

While the analysis of a non-randomised comparison group (PCRS data) provided a national context to the study, findings revealed no notable difference overall in prescribing behaviour by the control group compared to prescribing nationally, this is a non-randomised group and is therefore subject to confounding.

The external validity of this study may have limitations. GP recruitment was modest at 32%, comparing favourably to similar PIP related RCTs<sup>13</sup> but smaller than reported in other primary care studies.<sup>37</sup> When compared to a national sample of practices,<sup>38</sup> study practices had, on average, more GPs and public patients so may not be representative of practices nationally. However, the last available national data on GPs was from 2005 so may be somewhat out of date.<sup>38</sup>

### **Implications for practice and directions for future study**

The reduction in PIP in the OPTI-SCRIPT study may have important clinical and economic implications. Almost half of the intervention group were no longer exposed to PIP at intervention completion. While it cannot be assumed that a change in PIP necessitates a change in health outcomes,<sup>39,40</sup> reducing PIP potentially may decrease adverse outcomes such as ADEs and hospitalisations in older patients.<sup>5</sup> As the OPTI-SCRIPT study effect size was largely driven by proton pump inhibitor prescribing, the intervention may attenuate the risks associated with these drugs such as hip fractures and community acquired pneumonia.<sup>41,42</sup>

Reducing PIP related to proton pump inhibitor prescribing may also contribute to significant savings as an estimated €22 million was spent on potentially inappropriate proton pump inhibitors in 2007.<sup>43</sup>

Based on the positive findings presented here, further modelling of the intervention components is planned to determine the effectiveness of the OPTI-SCRIPT intervention long term and the potential impact it may have on cases of PIP other than for proton pump inhibitor prescribing.

PIP is an important public health concern that can result in increased morbidity, adverse drug events, hospitalisation and expenditure.<sup>2,7</sup> This study shows that the OPTI-SCRIPT intervention reduced PIP, primarily through a reduction in proton pump inhibitor prescribing, in a way that this is acceptable to both GPs and their patients. Tailoring of the intervention to impact more specifically on different cases of PIP is planned.



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## Tables

Table 1 Summary of OPTI-SCRIPT intervention and control groups

<b>Intervention</b>	<p>The intervention consisted of:</p> <ol style="list-style-type: none"> <li>1) Academic detailing with a pharmacist One session (30 minutes) where a pharmacist visited the practice to discuss PIP, medicines review and the web-based pharmaceutical treatment algorithms</li> <li>2) Medicines review with web-based pharmaceutical treatment algorithms. GPs were asked to conduct one review per patient using the web-based platform to guide them through the process. The GP was presented with the specific PIP drug(s) for each patient, and for each PIP drug, there was a treatment algorithm with the following structure: <ol style="list-style-type: none"> <li>a. The individual PIP with reason for concern</li> <li>b. Alternative pharmacological and non-pharmacological treatment options</li> <li>c. Background information (where relevant)</li> </ol> </li> <li>3) Patient information leaflets to give to patients during the review. Each leaflet: <ol style="list-style-type: none"> <li>a. Described the PIP and the reasons as to why it may be inappropriate</li> <li>b. Outlined the alternative pharmacological and non-pharmacological therapies GPs may offer.</li> </ol> </li> </ol>
<b>Control</b>	<p>Control practices delivered usual care. Usual care for public general medical services (GMS) patients allows GPs to give a prescription on a monthly or three monthly basis.</p> <p>Control practices received simple patient-level PIP postal feedback in the form of a list summarizing the medication class to which the individual patient's potentially inappropriate medication belonged.</p> <p>Control practices did not receive an academic detailing visit or were not prompted to carry out medicines review with the individual patients.</p>

*Abbreviations:* GMS (general medical services); PIP (potentially inappropriate prescribing)

Table 2 Baseline characteristics of practices and patients in intervention and control groups

Characteristic	Intervention N	Control N
<b>Practice factors</b>		
Number of practices (%)	11 (52.4)	10 (47.6)
GMS list size (%)		
- 500 or less	1 (9.1)	2 (20.0)
- 501- 1,500	3 (27.3)	2 (20.0)
- 1,501 and over	7 (63.6)	6 (60.0)
Practice with a manager	8 (72.8)	7 (70.0)
Location (%)		
- Urban <sup>^</sup>	8 (80.0)	8 (72.7)
- Mixed	3 (20.0)	2 (27.3)
Mean number of GPs per practice (SD)	4.1 (3.1)	4.1(2.1)
Mean number of patients over 70 per practice (SD)	712.1 (525.3)	788.2 (987.2)
Median deprivation score <sup>†</sup> (IQR)	0.5 (-0.3 to 1.6)	1.4 (0.3 to 2.4)
<b>Patient factors</b>		
Male (%)	55 (55.6)	50 (51.5)
Marital status (%)		
- Married	56 (56.6)	51 (53.1)
- Widowed	26 (26.3)	32 (33.3)
- Single	14 (14.1)	10 (10.4)
GMS card holder (SD)	88 (88.9)	95 (97.9)
Mean age (SD)	77.1 (4.9)	76.4 (4.8)
Mean number of repeat medications (SD)	10.2 (4.5)	9.5 (4.1)
PIP*		
- Mean (SD)	1.31 (0.6)	1.39 (0.6)
- Median (IQR)	1 (1 to 2)	1 (1 to 2)
<i>Most prevalent indicator: (%)</i>		
- Proton Pump Inhibitors	53 (53.3)	65 (67.7)

Figures are numbers (percentages) unless stated otherwise

<sup>^</sup> Urban area: relatively small centre of population, with 5,000 or more residents<sup>38</sup>

<sup>†</sup> Population weighted deprivation score for each practice - large values mean practices are situated in more socio-economically deprived areas

\* All patients had at least one potentially inappropriate prescription at baseline

*Abbreviations:* GMS (general medical services); IQR (Interquartile range);

PIP (potentially inappropriate prescribing); SD (Standard Deviation)

Table 3 Potentially inappropriate prescriptions at baseline in intervention and control groups

Potentially inappropriate prescription	Intervention (N = 99)		Control (N=97)	
	N	%	N	%
<b>Proton pump inhibitor at maximum therapeutic dosage for &gt;8 weeks</b>	53	53.3	65	67.7
<b>NSAIDs</b> Long terms use; interactions with certain medications e.g. diuretic	21	21.2	16	16.8
<b>Therapeutic duplication</b> Any regular duplicate drug class prescription, for example, two concurrent opiates, NSAIDs	19	19.2	13	13.5
<b>Long-term (i.e. &gt;1 month), long-acting benzodiazepines</b>	14	14.4	8	8.3
<b>Steroid without bisphosphonate</b>	9	9.1	4	4.2
<b>Bladder antimuscarinics</b> Contraindications and interactions with certain medications	1	1.0	9	9.4
<b>Prolonged use (i.e. &gt;1 week) of first-generation antihistamines</b>	4	4.0	2	2.1
<b>Tricyclic antidepressants (TCAs)</b> Contraindications and interactions with certain medications e.g. opiate, calcium channel blocker	1	1.0	5	5.2
<b>Thiazide diuretic with gout</b>	3	3.0	2	2.1
<b>Aspirin</b> Contraindications and interactions with certain medications e.g. warfarin	3	3.0	1	1.0
<b>Digoxin</b> Inappropriate dose	1	1.0	3	3.1
<b>Calcium channel blocker</b> Contraindications and interactions with certain medications	0	0.0	3	3.1

*Abbreviations:*

ns: NSAIDs (Nonsteroidal anti-inflammatory drug); TCAs (Tricyclic antidepressants);

Table 4 Intention to treat analysis of primary outcomes at immediate intervention completion

Characteristic	Intervention N (%)	Control N (%)	Adjusted* odds ratio (95% CI)	Adjusted* incident rate ratio (95% CI)	Mean difference *** (95% CI)	P value
Primary outcome: Proportion						
PIP at baseline	99 (100)	97 (100)	0.32 (0.15 to 0.70)	-	-	0.02
PIP at intervention completion	52 (52.5)	75 (77.3)				
No PIP at intervention completion	47 (47.5)	22 (22.7)				
Primary outcome: Mean						
Mean at baseline (SD)	1.31 (0.6)	1.39 (0.6)	-	-	- 0.48 (-0.80 to - 0.17)	0.02
Mean at intervention completion (SD)	0.70 (0.1)	1.18 (0.1)				
Additional outcome: Median						
Median at baseline (IQR)	1 (1 to 2)	1 (1 to 2)	-	-	-	-
Median at intervention completion (IQR)	1 (0 to 1)	1 (1 to 2)				
Additional outcome: Poisson regression						
PIP at baseline	99 (100)	97 (100)		0.71** (0.50 to 1.02)		0.49
PIP at intervention completion	52 (52.5)	75 (77.3)				
No PIP at intervention completion	47 (47.5)	22 (22.7)				

Figures are numbers (percentages) unless stated otherwise. The Bonferroni method was used to account for multiple comparisons.

\*Adjusted for age, gender, baseline number of PIP drugs, baseline number of repeat medications, number of GPs, practice location

\*\* Results from modelling the number of PIPs per person with Poisson regression adjusted for age, gender, baseline number of PIP drugs, baseline number of repeat medications, number of GPs, practice location

\*\*\* Results from unadjusted cluster level *t*-test

*Abbreviations:* CI (confidence interval); IQR (Interquartile range); PIP (potentially inappropriate prescribing); SD (Standard Deviation)



Table 5 Intention to treat analysis of secondary outcomes at immediate intervention completion

<b><i>Drug specific outcomes</i></b>				
<b>Characteristic</b>	<b>Intervention N (%)</b>	<b>Control N (%)</b>	<b>Adjusted* odds ratio (95% CI)</b>	<b>P value</b>
Proton pump inhibitor at baseline Proton pump inhibitor at intervention completion	53 (53.5) 23 (23.2)	65 (67.7) 46 (47.4)	0.30 (0.14 to 0.68)	0.04
Duplicate at baseline Duplicate at intervention completion	19 (19.2) 11 (11.1)	13 (13.5) 11 (11.3)	0.83 (0.32 to 2.13)	0.99
Long-term benzodiazepines at baseline Long-term benzodiazepines at intervention completion	14 (14.1) 9 (9.1)	8 (8.1) 9 (9.1)	1.31 (0.47 to 3.68)	0.99
<b><i>Patient reported outcomes</i></b>				
<b>Characteristic</b>	<b>Intervention</b>	<b>Control</b>	<b>Adjusted* mean difference (95% CI)</b>	<b>P value</b>
WBQ: Mean well-being <sup>^</sup> at baseline WBQ: Mean well-being <sup>^</sup> at intervention completion	24.3 23.6	24.4 24.0	- 0.41 (-1.80 to 1.07)	0.99
BMQ: Median necessity-concern differential <sup>†</sup> at baseline BMQ: Median necessity-concern differential <sup>†</sup> at baseline	7.0 6.0	6.0 5.8	0.16 (-1.85 to 1.07)	0.99

Figures are numbers (percentages) unless stated otherwise. The Bonferroni method was used to account for multiple comparisons.

\*Adjusted for age, gender, baseline number of PIP drugs, baseline number of repeat medications, number of GPs, practice location

<sup>^</sup>Well-being Score ranges from 0-36 (1-12 low, 13-24 medium, 25-36 high)

<sup>†</sup>Scale from -20-20 where positive scores indicate benefits outweigh risks

*Abbreviations:* BMQ (Beliefs about Medicine Questionnaire); CI (confidence interval); WBQ-12 (Well-being Questionnaire)

Table 6 Comparison of potentially inappropriate prescribing in the OPTI-SCRIPT study population to the national (PCRS) comparator

Numbers (percentages) of participants are presented, unless otherwise stated

PIP status	OPTI-SCRIPT intervention group	OPTI-SCRIPT control group	PCRS national comparator
Proportion with PIP			
PIP at baseline	99 (100)	97 (100)	103,261 (100)
PIP at intervention completion	52 (52.5)	75 (77.3)	75,401 (73.1)
No PIP at intervention completion	47 (47.5)	22 (22.7)	27,860 (26.9)
Crude odds ratio †	0.4 (95% CI 0.3 to 0.6)		
Decrease in PIP			
PIP at baseline	99 (100)	97 (100)	103,261 (100)
PIP stayed same or increased at intervention completion	42 (42.4)	65 (67.0)	67,188 (65.1)
Decrease in PIP at intervention completion	57 (57.6)	32 (32.9)	36,073 (34.9)
Crude odds ratio †	2.5 (95% CI 1.8 to 4.0)		

† The odds of PIP in the OPTI-SCRIPT intervention group compared to the odds in national PCRS comparator data

*Abbreviations:* CI (confidence interval); PCRS (primary care reimbursement services); PIP (potentially inappropriate prescribing);

## Appendices

### Appendix 1: Selected Prescribing Criteria/Prescribing Indicator

Criteria	Concern	Prevalence in Ireland*
PPI for peptic ulcer disease at full therapeutic dosage for >8 weeks	Earlier discontinuation or dose reduction for maintenance/ prophylactic treatment of peptic ulcer disease, oesophagitis or GORD is indicated	16.69%
NSAID (>3 months) for relief of mild joint pain in osteoarthritis	Simple analgesics are preferable and usually as effective for pain relief	8.76%
Long-term (i.e. >1 month), long-acting benzodiazepines, e.g. chlordiazepoxide, flurazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites e.g. diazepam	Risk of prolonged sedation, confusion, impaired balance, falls	5.22%
Any regular duplicate drug class prescription, e.g. 2 concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors. Excludes duplicate prescribing of drugs that may be required on a PRN basis, e.g. inhaled beta 2 agonists (long and short acting) for asthma or COPD, and opiates for management of breakthrough pain	Optimization of monotherapy within a single drug class should be observed prior to considering a new class of drug	4.78%
TCAs with an opiate or calcium channel blocker	Risk of severe constipation	2.05%
Aspirin at dosage >150 mg/day	Increased bleeding risk, no evidence for increased efficacy	1.69%
Theophylline as monotherapy for COPD/Asthma	Risk of adverse effects due to narrow therapeutic index	1.18%
Use of aspirin and warfarin in combination without histamine H <sub>2</sub> receptor antagonist (except cimetidine because of interaction with warfarin) or PPI	High risk of GI bleeding	1.09%
Doses of short-acting benzodiazepines, doses greater than: lorazepam (Ativan®), 3 mg; oxazepam (Serax®), 60 mg; alprazolam (Xanax®), 2 mg; temazepam (Restoril®), 15 mg; and triazolam (Halcion®), 0.25 mg	Total daily doses should rarely exceed the suggested maximums	1.54%
Prolonged use (>1 week) of first generation antihistamines, i.e. diphenhydramine, chlorpheniramine, cyclizine, promethazine	Risk of sedation and anticholinergic side-effects	0.96%
Warfarin and NSAID together	Risk of GI bleeding	0.75%

Calcium channel blockers with chronic constipation	May exacerbate constipation	0.68%
NSAID with history of peptic ulcer disease or GI bleeding, unless with concurrent histamine H <sub>2</sub> receptor antagonist, PPI or misoprostol	Risk of peptic ulcer relapse	0.67%
Bladder antimuscarinic drugs with dementia	Risk of increased confusion, agitation	0.46%
TCAs with constipation	May worsen constipation	0.45%
Digoxin at a long-term dosage >125 µg/day (with impaired renal function)	Increased risk of toxicity	0.36%
Thiazide diuretic with a history of gout	May exacerbate gout	0.36%
Glibenclamide (with type 2 diabetes mellitus)	Risk of prolonged hypoglycaemia	0.29%
Aspirin with a past history of peptic ulcer disease, without histamine H <sub>2</sub> receptor antagonist or PPI	Risk of bleeding	0.22%
Prochlorperazine (Stemetil®) or metoclopramide with Parkinsonism	Risk of exacerbating Parkinsonism	0.21%
TCAs with dementia	Risk of worsening cognitive impairment	0.18%
TCAs with glaucoma	Likely to exacerbate glaucoma	0.14%
TCAs with cardiac conductive abnormalities	Pro-arrhythmic effects	0.14%
Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis or osteoarthritis	Risk of major systemic corticosteroid side-effects	0.14%
Bladder antimuscarinic drugs with chronic prostatism	Risk of urinary retention	0.14%
NSAID with heart failure	Risk of exacerbation of heart failure	0.07%
TCAs with prostatism or prior history of urinary retention	Risk of urinary retention	0.07%
Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in COPD/Asthma	Unnecessary exposure to long-term side-effects of systemic steroids	0.07%
Bladder antimuscarinic drugs with chronic glaucoma	Risk of acute exacerbation of glaucoma	<0.01%
NSAID with SSRI	Increased risk of GI bleeding	N/A
Bladder antimuscarinic drugs with chronic	Risk of exacerbation of constipation	N/A

constipation		
Prednisolone (or equivalent) > 3 months or longer without bisphosphonate	Increased risk of fracture	N/A
NSAID with ACE-inhibitor	Risk of kidney failure, particularly with the presence of general arteriosclerosis, dehydration or concurrent use of diuretics	N/A
NSAID with diuretic	May reduce the effect of diuretics and worsen existing heart failure	N/A

*Abbreviations – ACEI (angiotensin-converting-enzyme inhibitor); COPD (chronic obstructive pulmonary disease); GI (gastro-intestinal); NA (not available); GORD (gastro-oesophageal reflux disease); NSAID (Nonsteroidal anti-inflammatory drug); PPI (Proton Pump Inhibitor); PRN (Pro re nata, as needed); SSRI (Selective serotonin reuptake inhibitor); TCA (Tricyclic Anti-depressant)*

*\*Prevalence – the proportion of the study population with 1 or more potentially inappropriate medications*

## Appendix 2 OPTI-SCRIPT Website materials

Table A2.1 OPTI-SCRIPT treatment algorithm example

Proton Pump Inhibitors (PPIs)
<b>Section A Potentially Inappropriate Prescription:</b> Full therapeutic dose >8/52 → Not indicated  Long term PPI use is associated with an increased risk of fractures and may be associated with an increased risk of Community Acquired Pneumonia and C. difficile diarrhoea

### Section B Alternatives:

Consider the following alternatives:

1. [Discontinuation or dose reduction for maintenance therapy and gastroprotection](#)
2. [Pharmacological Alternatives](#)

#### 1. Discontinuation or dose reduction for maintenance therapy and gastroprotection

PPI	Full therapeutic dose Inappropriate for >8/52	Maintenance Dose / Gastroprotection
Omeprazole	≥ 40mg / day	20mg / day
Esomeprazole	≥ 40 mg / day	20 mg / day
Lansoprazole	≥ 30 mg / day	15 mg / day
Pantoprazole	≥ 40 mg / day	20 mg / day
Rabeprazole	> 20 mg / day	10 - 20 mg / day

#### 2. Pharmacological Alternatives

Pharmacological Alternative	Dose Recommendations	Co-Admin with Alternative Not Recommended	Co-Admin Caution	Non-pharmacological Alternative
H2 antagonist	1. <a href="#">Ranitidine</a> , 150mg BD, maintenance dose 150-300mg daily			
Occasional reflux can be treated with OTC preparations	1. <a href="#">Gaviscon Advance</a> , 1-2 tabs or 5-10ml after meals and bedtime			

### Patient Information Leaflets:

PPIs for people with peptic ulcer disease, please click  
[http://hrbcentreprimarycare.ie/OPTISCRIP/Files/1\\_PPI\\_PUD.pdf](http://hrbcentreprimarycare.ie/OPTISCRIP/Files/1_PPI_PUD.pdf)

PPIs for people with gastro-oesophageal reflux disease (GORD), please click  
[http://hrbcentreprimarycare.ie/OPTISCRIP/Files/2\\_PPI\\_GORD.pdf](http://hrbcentreprimarycare.ie/OPTISCRIP/Files/2_PPI_GORD.pdf)

### Section C: Background Information

#### Managing gastro-oesophageal reflux disease (GORD)

- Offer a full-dose PPI (omeprazole 40mg/day) for 1 month to all people with endoscopically determined oesophagitis or endoscopy-negative reflux disease.
- Advise that symptoms may recur after stopping treatment, and to return for treatment if they experience persistent or recurrent symptoms.
- For those whose symptoms persist, offer a further month of full-dose PPI.
- For people with persistent, severe symptoms, consider a double-dose PPI (omeprazole 40mg bd) for a further month.
- For people with a particular problem with nocturnal symptoms that do not respond to PPI therapy, consider adding an H<sub>2</sub>-receptor antagonist at bedtime in the short term (e.g. intermittent 2-week courses of Ranitidine 150mg nocte).
- For people who do not respond to a second month of full-dose PPI or a month of double-dose PPI, consider a trial of treatment with an H<sub>2</sub>-receptor antagonist (ranitidine 150mg bd) or a prokinetic (domperidone 10mg tds) or referral for further management of refractory GORD.

#### Managing peptic ulcer disease (PUD)




- Test for *Helicobacter pylori* if this has not already been done.
- If the result is negative, treat with full-dose PPI (omeprazole 40mg/day) for 1 or 2 months, depending on the reported severity of ulceration.
- If the result is positive, prescribe eradication therapy (omeprazole 20mg bd + clarithromycin 500mg bd + amoxicillin 1g bd, all for 1 week).
- After at least four weeks of completing eradication therapy, re-test for *H. pylori*. Prescribe an alternative eradication therapy if the repeat test result is positive.
- For gastric ulcers, arrange repeat endoscopy 6–8 weeks after completing treatment.

#### Reducing risk of NSAID-associated ulceration

If NSAID therapy is absolutely necessary and the individual is aware of the risk of continuing treatment:

- Consider topical agent or prescribe low-dose ibuprofen (400 mg tds) with a PPI (omeprazole 20mg/day). Judgment of risk should include consideration of the individual's age and comorbidity, and the dose and frequency of NSAID used

Table A2.1 OPTI-SCRIPT patient information leaflet

<div data-bbox="231 436 805 638">  <h2>Information about your medicines: Proton Pump Inhibitors (PPI) for people with peptic ulcer disease</h2> </div> <div data-bbox="231 660 614 683"> <h3>What are proton pump inhibitors (PPIs)?</h3> </div> <div data-bbox="231 694 805 974"> <p>Proton pump inhibitors (PPIs) are a group of medicines that work on the cells that line the stomach, reducing the production of acid. They are commonly used to:</p> <ul style="list-style-type: none"> <li>• Reduce acid reflux which may cause heartburn or oesophagitis (inflammation of the gullet), these conditions are sometimes called gastro-oesophageal reflux disease or GORD</li> <li>• Treat ulcers in the stomach and duodenum (part of the gut)</li> <li>• Help prevent and treat ulcers associated with anti-inflammatory drugs called NSAIDs (non-steroidal anti-inflammatory drugs) which includes aspirin.</li> </ul> <p>PPIs usually work very well to reduce stomach acid and to treat the above conditions. In some cases your doctor may prescribe a PPI that you only take 'as required' to relieve your symptoms, rather than every day. In some cases a regular dose taken each day is advised, however this should be at a dose known as 'maintenance dose'. Higher doses of PPIs are no more effective than the maintenance doses in treating most of the conditions that these drugs are used for, however, they carry a higher risk of both long and short term side effects.</p> </div> <div data-bbox="231 996 558 1019"> <h3>What are the side effects of PPIs?</h3> </div> <div data-bbox="231 1030 805 1243"> <p>Side effects occur in a small number of PPI users. Possible side effects vary between different medicines. The leaflet that comes in the medicine packet gives a full list of possible side effects. Possible side effects include:</p> <ul style="list-style-type: none"> <li>• Constipation</li> <li>• Diarrhoea</li> <li>• Headaches</li> <li>• Nausea (feeling sick)</li> <li>• Abdominal (tummy) pain</li> <li>• Vomiting.</li> </ul> </div>	<div data-bbox="885 436 1460 492">  <h2>Information about your medicines: Proton Pump Inhibitors (PPI) for people with peptic ulcer disease</h2> </div> <div data-bbox="885 504 1165 593"> <p>Long-term use of PPIs may increase the risk of:</p> <ul style="list-style-type: none"> <li>• Bone fractures</li> <li>• Pneumonia</li> <li>• Clostridium difficile infection.</li> </ul> </div> <div data-bbox="885 616 1348 638"> <h3>What are the alternatives your doctor may offer?</h3> </div> <div data-bbox="885 649 1460 683"> <p>Your GP may recommend a number of different treatments for peptic ulcer disease. Some may be medications and some may not involve medications.</p> </div> <div data-bbox="885 716 997 739"> <h4>Other medicines</h4> </div> <div data-bbox="885 739 1460 795"> <p>Your GP may recommend a lower maintenance dose of a PPI. Alternatively, they may switch you to a H2 antagonist (a medicine which reduces the production of stomach acid) instead.</p> </div> <div data-bbox="885 817 1045 840"> <h4>Alternatives to medicine</h4> </div> <div data-bbox="885 840 1460 884"> <p>Your GP may refer you to be tested for a bacteria called <i>Helicobacter pylori</i> (if this has not already been done). If a positive result is found, a treatment for getting rid of the bacteria will be started.</p> </div> <div data-bbox="885 974 1165 1209"> <p>This information has been provided by the HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland (RCSI) as part of the OPTI-SCRIPT study - Optimizing Prescribing for Older People in Primary Care: a cluster randomized controlled trial. For further information on this study, please contact: Barbara Clyne HRB PhD Scholars Programme in Health Services Research, Royal College of Surgeons in Ireland (RCSI), Beaux Lane House, Lower Mercer Street, Dublin 2. T: +353 1 4072720 E: <a href="mailto:barbaraclyne@rcsi.ie">barbaraclyne@rcsi.ie</a></p> </div> <div data-bbox="885 1220 933 1243"> <p>Page 2</p> </div> <div data-bbox="1181 1108 1460 1243">  </div>
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